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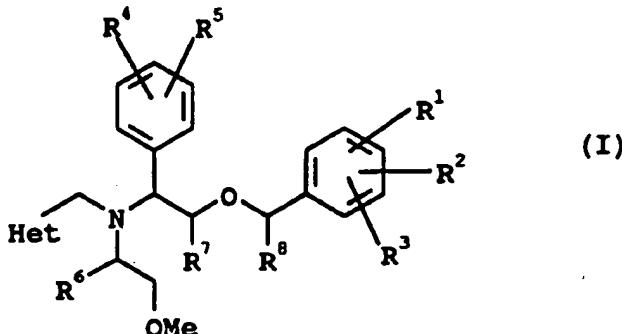
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(54) Title: AROMATIC COMPOUNDS USEFUL AS TACHYKININ ANTAGONISTS

(57) Abstract

The present invention relates to compounds of formula (I), wherein R¹ and R⁴ represent hydrogen, halogen, C₁-alkyl, C₂-alkenyl, C₂-alkynyl, C₃-cycloalkyl, C₃-cycloalkyl/C₁-alkyl, C₁-alkoxy, C₁-alkyl substituted by a hydroxy or C₁-alkoxy group, OCF₃, hydroxy, trifluoromethyl, trimethylsilyl, nitro, CN, SR^a, SOR^a, SO₂R^a, COR^a, CO₂R^a or CONR^aR^b where R^a and R^b are each independently hydrogen or C₁-alkyl; R², R³ and R⁵ represent hydrogen, halogen, C₁-alkyl, C₁-alkoxy substituted by a C₁-alkoxy group, or trifluoromethyl; R⁶, R⁷ and R⁸ each independently represent hydrogen or a C₁-alkyl group optionally substituted by a hydroxy group; and Het represents a 5- or 6-membered heterocyclic ring containing 2 or 3 nitrogen atoms optionally substituted by -O-, -S or a C₁-alkyl group, and optionally substituted by a group of the formula ZNR⁹R¹⁰. The compounds are of particular use in the treatment of pain, inflammation, migraine and emesis.



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AROMATIC COMPOUNDS USEFUL AS TACHYKININ ANTAGONISTS

This invention relates to a class of heteroaromatic compounds which
5 are useful as tachykinin antagonists.

The tachykinins are a group of naturally occurring peptides found widely distributed throughout mammalian tissues, both within the central nervous system and in peripheral nervous and circulatory systems.

10 The tachykinins are distinguished by a conserved carboxyl-terminal sequence:

Phe-X-Gly-Leu-Met-NH₂

At present, there are three known mammalian tachykinins referred to as substance P, neurokinin A (NKA, substance K, neuromedin L) and neurokinin B (NKB, neuromedin K) (for review see J.E. Maggio, *Peptides* 15 (1985) 6(suppl. 3), 237-242). The current nomenclature designates the three tachykinin receptors mediating the biological actions of substance P, NKA and NKB as the NK₁, NK₂ and NK₃ receptors, respectively.

Evidence for the usefulness of tachykinin receptor antagonists in pain, headache, especially migraine, Alzheimer's disease, multiple 20 sclerosis, attenuation of morphine withdrawal, cardiovascular changes, oedema, such as oedema caused by thermal injury, chronic inflammatory diseases such as rheumatoid arthritis, asthma/bronchial hyperreactivity and other respiratory diseases including allergic rhinitis, inflammatory diseases of the gut including ulcerative colitis and Crohn's disease, ocular 25 injury and ocular inflammatory diseases, proliferative vitreoretinopathy, irritable bowel syndrome and disorders of bladder function including cystitis and bladder detrusor hyper-reflexia is reviewed in "Tachykinin Receptors and Tachykinin Receptor Antagonists", C.A. Maggi, R. Patacchini, P. Rovero and A. Giachetti, *J. Auton. Pharmacol.* (1993) 13, 30 23-93.

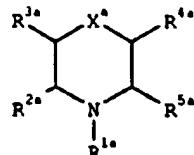
For instance, substance P is believed inter alia to be involved in the neurotransmission of pain sensations [Otsuka *et al*, "Role of Substance P as a Sensory Transmitter in Spinal Cord and Sympathetic Ganglia" in 1982 *Substance P in the Nervous System*, Ciba Foundation Symposium 91, 5 13-34 (published by Pitman) and Otsuka and Yanagisawa, "Does Substance P Act as a Pain Transmitter?" *TIPS* (1987) 8, 506-510], specifically in the transmission of pain in migraine (B.E.B. Sandberg *et al*, *J. Med Chem.*, (1982) 25, 1009) and in arthritis [Levine *et al* *Science* (1984) 10 226, 547-549]. Tachykinins have also been implicated in gastrointestinal (GI) disorders and diseases of the GI tract such as inflammatory bowel disease [Mantyh *et al* *Neuroscience* (1988) 25(3), 817-37 and D. Regoli in "Trends in Cluster Headache" Ed. Sicuteri *et al* Elsevier Scientific Publishers, Amsterdam (1987) page 85] and emesis [F. D. Tattersall *et al*, *Eur. J. Pharmacol.*, (1993) 250, R5-R6]. It is also hypothesised that there 15 is a neurogenic mechanism for arthritis in which substance P may play a role [Kidd *et al* "A Neurogenic Mechanism for Symmetrical Arthritis" in *The Lancet*, 11 November 1989 and Grönblad *et al*, "Neuropeptides in Synovium of Patients with Rheumatoid Arthritis and Osteoarthritis" in *J. Rheumatol.* (1988) 15(12), 1807-10]. Therefore, substance P is believed to 20 be involved in the inflammatory response in diseases such as rheumatoid arthritis and osteoarthritis, and fibrositis [O'Byrne *et al*, *Arthritis and Rheumatism* (1990) 33, 1023-8]. Other disease areas where tachykinin antagonists are believed to be useful are allergic conditions [Hamelet *et al*, *Can. J. Pharmacol. Physiol.* (1988) 66, 1361-7], immunoregulation [Lotz *et al*, *Science* (1988) 241, 1218-21 and Kimball *et al*, *J. Immunol.* (1988) 25 141(10), 3564-9] vasodilation, bronchospasm, reflex or neuronal control of the viscera [Mantyh *et al*, *PNAS* (1988) 85, 3235-9] and, possibly by arresting or slowing β -amyloid-mediated neurodegenerative changes [Yankner *et al*, *Science* (1990) 250, 279-82] in senile dementia of the 30 Alzheimer type, Alzheimer's disease and Down's Syndrome.

Tachykinin antagonists may also be useful in the treatment of small cell carcinomas, in particular small cell lung cancer (SCLC) [Langdon *et al*, *Cancer Research* (1992) **52**, 4554-7].

Substance P may also play a role in demyelinating diseases such as 5 multiple sclerosis and amyotrophic lateral sclerosis [J. Luber-Narod *et al*, poster *C.I.N.P. XVIIth Congress*, 28th June-2nd July 1992], and in disorders of bladder function such as bladder detrusor hyper-reflexia (*Lancet*, 16th May 1992, 1239).

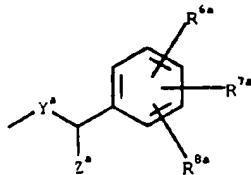
It has furthermore been suggested that tachykinins have utility in 10 the following disorders: depression, dysthymic disorders, chronic obstructive airways disease, hypersensitivity disorders such as poison ivy, vasospastic diseases such as angina and Reynaud's disease, fibrosing and collagen diseases such as scleroderma and eosinophilic fascioliasis, reflex sympathetic dystrophy such as shoulder/hand syndrome, addiction 15 disorders such as alcoholism, stress related somatic disorders, neuropathy, neuralgia, disorders related to immune enhancement or suppression such as systemic lupus erythematosus (European patent specification no. 0 436 334), ophthalmic disease such as conjunctivitis, vernal conjunctivitis, and the like, and cutaneous diseases such as contact dermatitis, atopic 20 dermatitis, urticaria, and other eczematoid dermatitis (European patent specification no. 0 394 989).

European patent specification no. 0 577 394 (published 5th January 1994) discloses morpholine and thiomorpholine tachykinin receptor antagonists of the general formula



25

wherein R^{1a} is a large variety of substituents;
R^{2a} and R^{3a} are *inter alia* hydrogen;
R^{4a} is *inter alia*



R^{5a} is *inter alia* optionally substituted phenyl;

R^{6a}, R^{7a} and R^{8a} are a variety of substituents;

X^a is O, S, SO or SO₂;

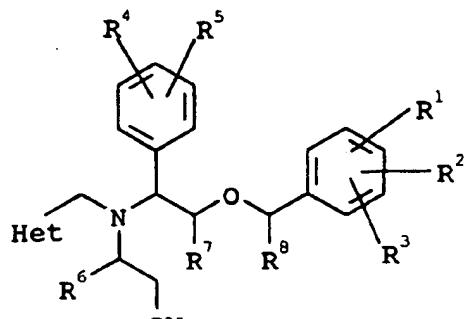
5 Y^a is *inter alia* O; and

Z^a is hydrogen or C₁₋₄alkyl.

We have now found a further class of non-peptides which are potent antagonists of tachykinins, especially of substance P.

The present invention provides compounds of the formula (I):

10



(I)

wherein

R¹ represents hydrogen, halogen, C₁₋₆alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl,

15 C₃₋₇cycloalkyl, C₃₋₇cycloalkylC₁₋₄alkyl, C₁₋₆alkoxy, C₁₋₄alkyl substituted by a hydroxy or C₁₋₄alkoxy group, OCF₃, hydroxy, trifluoromethyl,

trimethylsilyl, nitro, CN, SR^b, SOR^b, SO₂R^b, COR^b, CO₂R^b or CONR^aR^b

where R^a and R^b are each independently hydrogen or C₁₋₄alkyl;

R² and R³ each independently represent hydrogen, halogen,

20 C₁₋₆alkyl, C₁₋₆alkoxy substituted by a C₁₋₄alkoxy group, or trifluoromethyl;

R⁴ represents hydrogen, halogen, C₁₋₆alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, C₃₋₇cycloalkyl, C₃₋₇cycloalkylC₁₋₄alkyl, C₁₋₆alkoxy, C₁₋₄alkyl substituted by a hydroxy or C₁₋₄alkoxy group, OCF₃, hydroxy, trifluoromethyl, trimethylsilyl, nitro, CN, SR^a, SOR^a, COR^a, CO₂R^a, CONR^aR^b where 5 R^a and R^b are as previously defined;

R⁵ represents hydrogen, halogen, C₁₋₆alkyl, C₁₋₆alkoxy substituted by a C₁₋₄alkoxy group, or trifluoromethyl;

R⁶, R⁷ and R⁸ each independently represent hydrogen or a C₁₋₄alkyl group optionally substituted by a hydroxy group;

Het represents a 5- or 6-membered heterocyclic ring containing 2 or 10 3 nitrogen atoms optionally substituted by =O, =S or a C₁₋₄alkyl group, and optionally substituted by a group of the formula ZNR⁹R¹⁰ where

Z is C₁₋₆alkylene or C₃₋₆cycloalkyl;

R⁹ is hydrogen or C₁₋₄alkyl, C₃₋₇cycloalkyl,

15 C₃₋₇cycloalkylC₁₋₄alkyl, or C₂₋₄alkyl substituted by C₁₋₄alkoxy or hydroxyl;

R¹⁰ is hydrogen or C₁₋₄alkyl, C₃₋₇cycloalkyl,

C₃₋₇cycloalkylC₁₋₄alkyl, or C₂₋₄alkyl substituted by C₁₋₄alkoxy, hydroxyl or a 4, 5 or 6 membered heteroaliphatic ring containing one or two heteroatoms selected from N, O and S;

20 or R⁹, R¹⁰ and the nitrogen atom to which they are attached form a heteroaliphatic ring of 4 to 7 ring atoms, optionally substituted by one or two groups selected from hydroxy or C₁₋₄alkoxy optionally substituted by a C₁₋₄alkoxy or hydroxyl group, and optionally containing a double bond, which ring may optionally contain an oxygen or sulphur ring atom, a

25 group S(O) or S(O)₂ or a second nitrogen atom which will be part of a NH or NR^c moiety where R^c is C₁₋₄alkyl optionally substituted by hydroxy or C₁₋₄alkoxy;

or R⁹, R¹⁰ and the nitrogen atom to which they are attached form a non-aromatic azabicyclic ring system of 6 to 12 ring atoms;

or Z, R⁹ and the nitrogen atom to which they are attached form a heteroaliphatic ring to 4 to 7 ring atoms which may optionally contain an oxygen ring atom;

and pharmaceutically acceptable salts thereof.

5 Certain particularly apt compounds of the present invention include those wherein R¹ is hydrogen, C₁₋₄alkyl, C₁₋₄alkoxy, halogen or CF₃.

Most aptly R² is hydrogen, C₁₋₄alkyl, C₁₋₄alkoxy, halogen or CF₃.

Most aptly R³ is hydrogen, fluorine, chlorine or CF₃.

Favourably R¹ is fluorine, chlorine or CF₃.

10 Favourably R² is hydrogen, fluorine, chlorine or CF₃.

Favourably R³ is hydrogen, fluorine, chlorine or CF₃.

Preferably R¹ and R² are in the 3 and 5 positions of the phenyl ring.

More preferably, R¹ is 3-fluoro or 3-CF₃.

More preferably, R² is 5-fluoro or 5-CF₃.

15 More preferably, R³ is hydrogen.

Most preferably, R¹ is 3-F or 3-CF₃, R² is 5-F or 5-CF₃ and R³ is hydrogen.

Most aptly R⁴ is hydrogen.

Most aptly R⁵ is hydrogen, fluorine, chlorine or CF₃.

20 Preferably R⁴ is hydrogen and R⁵ is hydrogen or 4-fluoro.

Most aptly R⁶ and R⁷ are each independently hydrogen or methyl.

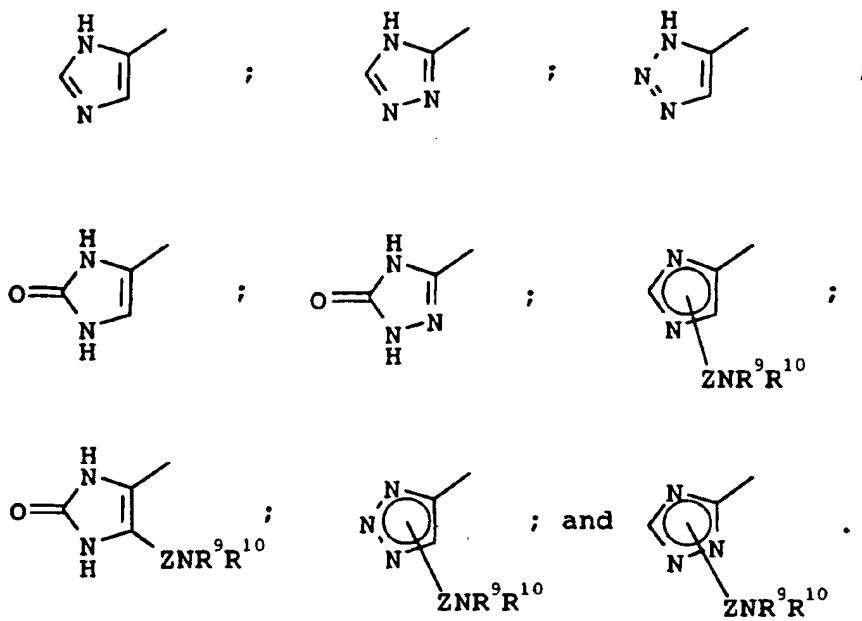
Preferably R⁶ is hydrogen. Preferably R⁷ is hydrogen. Most

preferably R⁶ and R⁷ are both hydrogen.

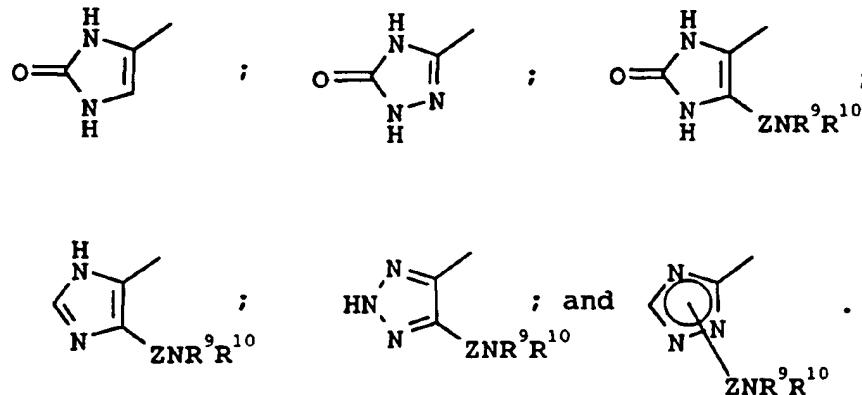
25 Most aptly R⁸ may be hydrogen or C₁₋₂alkyl optionally substituted by a hydroxy group. In particular, R⁸ may be hydrogen, methyl or hydroxymethyl.

Favourably Het is a 5-membered ring.

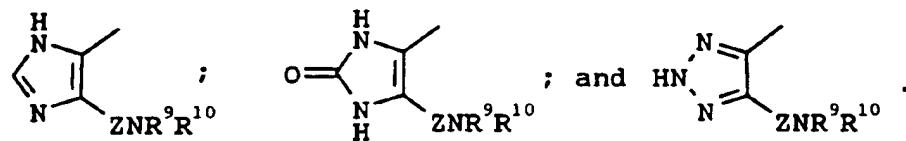
In particular, Het may represent a heterocyclic ring selected from:



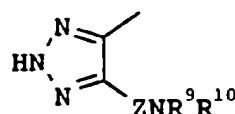
Particularly preferred heterocyclic rings represented by R⁶ are selected from:



5 Most especially, Het may represent a heterocyclic ring selected from:



A particularly preferred heterocyclic ring represented by Het is:



With respect to compounds of the formula (I), Z may be a linear, branched or cyclic group. Favourably Z contains 1 to 4 carbon atoms and 5 most favourably 1 or 2 carbon atoms. A particularly favourable group Z is CH₂.

With respect to compounds of the formula (I), R⁹ may aptly be a C₁-alkyl group or a C₂₋₄-alkyl group substituted by a hydroxyl or C₁₋₂-alkoxy group, R¹⁰ may aptly be a C₁₋₄-alkyl group or a C₁₋₄-alkyl group substituted 10 by a hydroxyl or C₁₋₂-alkoxy group, or R⁹ and R¹⁰ may be linked so that, together with the nitrogen atom to which they are attached, they form an azetidinyl, pyrrolidinyl, piperidyl, morpholino, thiomorpholino, piperazino or piperazino group substituted on the nitrogen atom by a C₁₋₄-alkyl group or a C₂₋₄-alkyl group substituted by a hydroxy or C₁₋₂-alkoxy group.

Where the group NR⁹R¹⁰ represents a heteroaliphatic ring of 4 to 7 ring atoms and said ring contains a double bond, a particularly preferred group is 3-pyrroline.

Where the group NR⁹R¹⁰ represents a non-aromatic azabicyclic ring system, such a system may contain between 6 and 12, and preferably 20 between 7 and 10, ring atoms. Suitable rings include 5-azabicyclo[2.1.1]hexyl, 5-azabicyclo[2.2.1]heptyl, 6-azabicyclo[3.2.1]octyl, 2-azabicyclo[2.2.2]octyl, 6-azabicyclo[3.2.2]nonyl, 6-azabicyclo[3.3.1]nonyl, 6-azabicyclo[3.2.2]decyl, 7-azabicyclo[4.3.1]decyl, 7-azabicyclo[4.4.1]undecyl and 8-azabicyclo[5.4.1]dodecyl, especially 25 5-azabicyclo[2.2.1]heptyl and 6-azabicyclo[3.2.1]octyl.

Where R¹⁰ represents a C₂₋₄-alkyl group substituted by a 5 or 6 membered heteroaliphatic ring containing one or two heteroatoms selected from N, O and S, suitable rings include pyrrolidino, piperidino, piperazino, morpholino, or thiomorpholino. Particularly preferred are nitrogen

containing heteroaliphatic rings, especially pyrrolidino and morpholino rings.

Particularly suitable moieties ZNR⁹R¹⁰ include those wherein Z is CH₂ or CH₂CH₂ and NR⁹R¹⁰ is amino, methylamino, dimethylamino, diethylamino, azetidinyl, pyrrolidino and morpholino.

Further preferred moieties represented by ZNR⁹R¹⁰ are those wherein Z is CH₂ or CH₂CH₂, R⁹ represents hydrogen, C₁₋₄alkyl or C₃₋₆cycloalkyl and R¹⁰ is C₂₋₄alkyl substituted by one or two substituents selected from hydroxy, C₁₋₂alkoxy, azetidinyl, pyrrolidino, piperidino, morpholino or thiomorpholino.

In particular, Z is preferably CH₂ and NR⁹R¹⁰ is preferably dimethylamino, azetidinyl or pyrrolidino, especially dimethylamino.

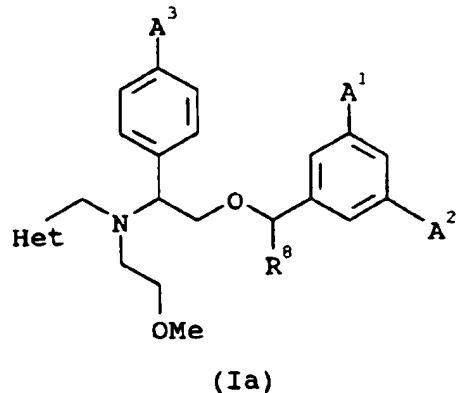
As used herein, the term "alkyl" or "alkoxy" as a group or part of a group means that the group is straight or branched. Examples of suitable alkyl groups include methyl, ethyl, n-propyl, i-propyl, n-butyl, s-butyl and t-butyl. Examples of suitable alkoxy groups include methoxy, ethoxy, n-propoxy, i-propoxy, n-butoxy, s-butoxy and t-butoxy.

The cycloalkyl groups referred to herein may represent, for example, cyclopropyl, cyclobutyl, cyclopentyl or cyclohexyl. A suitable cycloalkylalkyl group may be, for example, cyclopropylmethyl.

As used herein, the terms "alkenyl" and "alkynyl" as a group or part of a group means that the group is straight or branched. Examples of suitable alkenyl groups include vinyl and allyl. A suitable alkynyl group is propargyl.

When used herein the term halogen means fluorine, chlorine, bromine and iodine. The most apt halogens are fluorine and chlorine of which fluorine is preferred.

One favoured group of compounds of the present invention are of the formula (Ia):



wherein R⁸ and Het are as defined in relation to formula (I) and

A¹ is fluorine or CF₃;

5 A² is fluorine or CF₃; and

A³ is hydrogen or fluorine;

and pharmaceutically acceptable salts thereof.

Specific compounds within the scope of this invention include:

4-(N-((2-((3,5-bis(trifluoromethyl)phenyl)methoxy)-1-(S)-phenyl)ethyl-N-

10 (2'-methoxyethyl)aminomethyl)-5-(N,N'-dimethylaminomethyl)-1,2,3-triazole;

and pharmaceutically acceptable salts thereof.

In a further aspect of the present invention, the compounds of formula (I) will preferably be prepared in the form of a pharmaceutically acceptable salt, especially an acid addition salt.

For use in medicine, the salts of the compounds of formula (I) will be non-toxic pharmaceutically acceptable salts. Other salts may, however, be useful in the preparation of the compounds according to the invention or of their non-toxic pharmaceutically acceptable salts. Suitable

20 pharmaceutically acceptable salts of the compounds of this invention include acid addition salts which may, for example, be formed by mixing a solution of the compound according to the invention with a solution of a pharmaceutically acceptable acid such as hydrochloric acid, fumaric acid, p-toluenesulphonic acid, maleic acid, succinic acid, acetic acid, citric acid,

tartaric acid, carbonic acid, phosphoric acid or sulphuric acid. Salts of amine groups may also comprise quaternary ammonium salts in which the amino nitrogen atom carries a suitable organic group such as an alkyl, alkenyl, alkynyl or aralkyl moiety. Furthermore, where the compounds of 5 the invention carry an acidic moiety, suitable pharmaceutically acceptable salts thereof may include metal salts such as alkali metal salts, e.g. sodium or potassium salts; and alkaline earth metal salts, e.g. calcium or magnesium salts.

The salts may be formed by conventional means, such as by reacting 10 the free base form of the product with one or more equivalents of the appropriate acid in a solvent or medium in which the salt is insoluble, or in a solvent such as water which is removed *in vacuo* or by freeze drying or by exchanging the anions of an existing salt for another anion on a suitable ion exchange resin.

15 The present invention includes within its scope prodrugs of the compounds of formula (I) above. In general, such prodrugs will be functional derivatives of the compounds of formula (I) which are readily convertible *in vivo* into the required compound of formula (I).

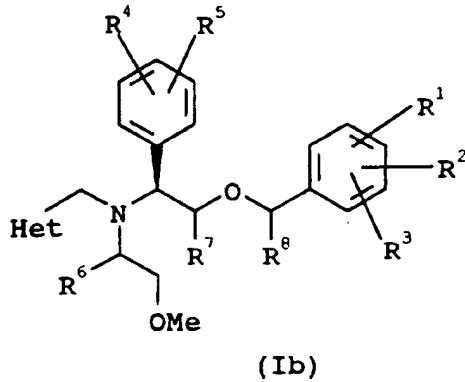
Conventional procedures for the selection and preparation of suitable 20 prodrug derivatives are described, for example, in "Design of Prodrugs", ed. H. Bundgaard, Elsevier, 1985.

A prodrug may be a pharmacologically inactive derivative of a biologically active substance (the "parent drug" or "parent molecule") that requires transformation within the body in order to release the active 25 drug, and that has improved delivery properties over the parent drug molecule. The transformation *in vivo* may be, for example, as the result of some metabolic process, such as chemical or enzymatic hydrolysis of a carboxylic, phosphoric or sulphate ester, or reduction or oxidation of a susceptible functionality.

30 The present invention includes within its scope solvates of the compounds of formula (I) and salts thereof, for example, hydrates.

The compounds according to the invention have at least three asymmetric centres, and may accordingly exist both as enantiomers and as diastereoisomers. It is to be understood that all such isomers and mixtures thereof are encompassed within the scope of the present
5 invention.

The preferred compounds of the formula (I) will have the preferred stereochemistry as shown in formula (Ib)



10

The present invention further provides pharmaceutical compositions comprising one or more compounds of formula (I) in association with a pharmaceutically acceptable carrier or excipient.

Preferably the compositions according to the invention are in unit
15 dosage forms such as tablets, pills, capsules, powders, granules, solutions or suspensions, or suppositories, for oral, parenteral or rectal administration, or administration by inhalation or insufflation.

For preparing solid compositions such as tablets, the principal active ingredient is mixed with a pharmaceutical carrier, e.g. conventional
20 tableting ingredients such as corn starch, lactose, sucrose, sorbitol, talc, stearic acid, magnesium stearate, dicalcium phosphate or gums, and other pharmaceutical diluents, e.g. water, to form a solid preformulation composition containing a homogeneous mixture of a compound of the present invention, or a non-toxic pharmaceutically acceptable salt thereof.

When referring to these preformulation compositions as homogeneous, it is meant that the active ingredient is dispersed evenly throughout the composition so that the composition may be readily subdivided into equally effective unit dosage forms such as tablets, pills and capsules.

- 5 This solid preformulation composition is then subdivided into unit dosage forms of the type described above containing from 0.1 to about 500 mg of the active ingredient of the present invention. The tablets or pills of the novel composition can be coated or otherwise compounded to provide a dosage form affording the advantage of prolonged action. For example,
- 10 the tablet or pill can comprise an inner dosage and an outer dosage component, the latter being in the form of an envelope over the former. The two components can be separated by an enteric layer which serves to resist disintegration in the stomach and permits the inner component to pass intact into the duodenum or to be delayed in release. A variety of
- 15 materials can be used for such enteric layers or coatings, such materials including a number of polymeric acids and mixtures of polymeric acids with such materials as shellac, cetyl alcohol and cellulose acetate.

- The liquid forms in which the novel compositions of the present invention may be incorporated for administration orally or by injection
- 20 include aqueous solutions, suitably flavoured syrups, aqueous or oil suspensions, and flavoured emulsions with edible oils such as cottonseed oil, sesame oil, coconut oil or peanut oil, as well as elixirs and similar pharmaceutical vehicles. Suitable dispersing or suspending agents for aqueous suspensions include synthetic and natural gums such as
- 25 tragacanth, acacia, alginates, dextran, sodium carboxymethylcellulose, methylcellulose, polyvinyl-pyrrolidone or gelatin.

- Preferred compositions for administration by injection include those comprising a compound of formula (I), as the active ingredient, in association with a surface-active agent (or wetting agent or surfactant) or
- 30 in the form of an emulsion (as a water-in-oil or oil-in-water emulsion).

Suitable surface-active agents include, in particular, non-ionic agents, such as polyoxyethylenesorbitans (e.g. Tween™ 20, 40, 60, 80 or 85) and other sorbitans (e.g. Span™ 20, 40, 60, 80 or 85). Compositions with a surface-active agent will conveniently comprise between 0.05 and 5% surface-active agent, and preferably between 0.1 and 2.5%. It will be appreciated that other ingredients may be added, for example mannitol or other pharmaceutically acceptable vehicles, if necessary.

Suitable emulsions may be prepared using commercially available fat emulsions, such as Intralipid™, Liposyn™, Infonutrol™, Lipofundin™ and Lipiphysan™. The active ingredient may be either dissolved in a pre-mixed emulsion composition or alternatively it may be dissolved in an oil (e.g. soybean oil, safflower oil, cottonseed oil, sesame oil, corn oil or almond oil) and an emulsion formed upon mixing with a phospholipid (e.g. egg phospholipids, soybean phospholipids or soybean lecithin) and water. 10
It will be appreciated that other ingredients may be added, for example glycerol or glucose, to adjust the tonicity of the emulsion. Suitable emulsions will typically contain up to 20% oil, for example, between 5 and 20%. The fat emulsion will preferably comprise fat droplets between 0.1 and 1.0µm, particularly 0.1 and 0.5µm, and have a pH in the range of 5.5 15
to 8.0.
20

Particularly preferred emulsion compositions are those prepared by mixing a compound of formula (I) with Intralipid™ or the components thereof (soybean oil, egg phospholipids, glycerol and water).

Compositions for inhalation or insufflation include solutions and 25 suspensions in pharmaceutically acceptable, aqueous or organic solvents, or mixtures thereof, and powders. The liquid or solid compositions may contain suitable pharmaceutically acceptable excipients as set out above. Preferably the compositions are administered by the oral or nasal respiratory route for local or systemic effect. Compositions in preferably 30 sterile pharmaceutically acceptable solvents may be nebulised by use of inert gases. Nebulised solutions may be breathed directly from the

nebulising device or the nebulising device may be attached to a face mask, tent or intermittent positive pressure breathing machine. Solution, suspension or powder compositions may be administered, preferably orally or nasally, from devices which deliver the formulation in an appropriate 5 manner.

The present invention further provides a process for the preparation of a pharmaceutical composition comprising a compound of formula (I), which process comprises bringing a compound of formula (I) into association with a pharmaceutically acceptable carrier or excipient.

10 The compounds of formula (I) are of value in the treatment of a wide variety of clinical conditions which are characterised by the presence of an excess of tachykinin, in particular substance P, activity.

Thus, for example, an excess of tachykinin, and in particular substance P, activity is implicated in a variety of disorders of the central 15 nervous system. Such disorders include mood disorders, such as depression or more particularly depressive disorders, for example, single episodic or recurrent major depressive disorders and dysthymic disorders, or bipolar disorders, for example, bipolar I disorder, bipolar II disorder and cyclothymic disorder; anxiety disorders, such as panic disorder with or 20 without agoraphobia, agoraphobia without history of panic disorder, specific phobias, for example, specific animal phobias, social phobias, obsessive-compulsive disorder, stress disorders including post-traumatic stress disorder and acute stress disorder, and generalised anxiety disorders; schizophrenia and other psychotic disorders, for example, 25 schizophreniform disorders, schizoaffective disorders, delusional disorders, brief psychotic disorders, shared psychotic disorders and psychotic disorders with delusions or hallucinations; delerium, dementia, and amnestic and other cognitive or neurodegenerative disorders, such as Alzheimer's disease, senile dementia, dementia of the Alzheimer's type, 30 vascular dementia, and other dementias, for example, due to HIV disease, head trauma, Parkinson's disease, Huntington's disease, Pick's disease,

Creutzfeldt-Jakob disease, or due to multiple aetiologies; Parkinson's disease and other extra-pyramidal movement disorders such as medication-induced movement disorders, for example, neuroleptic-induced parkinsonism, neuroleptic malignant syndrome, neuroleptic-induced acute 5 dystonia, neuroleptic-induced acute akathisia, neuroleptic-induced tardive dyskinesia and medication-induced postural tremour; substance-related disorders arising from the use of alcohol, amphetamines (or amphetamine-like substances) caffeine, cannabis, cocaine, hallucinogens, inhalants and aerosol propellants, nicotine, opioids, phenylglycidine derivatives, 10 sedatives, hypnotics, and anxiolytics, which substance-related disorders include dependence and abuse, intoxication, withdrawal, intoxication delerium, withdrawal delerium, persisting dementia, psychotic disorders, mood disorders, anxiety disorders, sexual dysfunction and sleep disorders; epilepsy; Down's syndrome; demyelinating diseases such as MS and ALS 15 and other neuropathological disorders such as peripheral neuropathy, for example diabetic and chemotherapy-induced neuropathy, and postherpetic neuralgia, trigeminal neuralgia, segmental or intercostal neuralgia and other neuralgias; and cerebral vascular disorders due to acute or chronic cerebrovascular damage such as cerebral infarction, subarachnoid 20 haemorrhage or cerebral oedema.

Tachykinin, and in particular substance P, activity is also involved in nociception and pain. The compounds of the present invention will therefore be of use in the prevention or treatment of diseases and conditions in which pain predominates, including soft tissue and 25 peripheral damage, such as acute trauma, osteoarthritis, rheumatoid arthritis, musculo-skeletal pain, particularly after trauma, spinal pain, myofascial pain syndromes, headache, episiotomy pain, and burns; deep and visceral pain, such as heart pain, muscle pain, eye pain, orofacial pain, for example, odontalgia, abdominal pain, gynaecological pain, for 30 example, dysmenorrhoea, and labour pain; pain associated with nerve and root damage, such as pain associated with peripheral nerve disorders, for

example, nerve entrapment and brachial plexus avulsions, amputation, peripheral neuropathies, tic douloureux, atypical facial pain, nerve root damage, and arachnoiditis; pain associated with carcinoma, often referred to as cancer pain; central nervous system pain, such as pain due to spinal 5 cord or brain stem damage; low back pain; sciatica; ankylosing spondylitis, gout; and scar pain.

Tachykinin, and in particular substance P, antagonists may also be of use in the treatment of respiratory diseases, particularly those associated with excess mucus secretion, such as chronic obstructive 10 airways disease, bronchopneumonia, chronic bronchitis, cystic fibrosis and asthma, adult respiratory distress syndrome, and bronchospasm; inflammatory diseases such as inflammatory bowel disease, psoriasis, fibrositis, osteoarthritis, rheumatoid arthritis, pruritis and sunburn; allergies such as eczema and rhinitis; hypersensitivity disorders such as 15 poison ivy; ophthalmic diseases such as conjunctivitis, vernal conjunctivitis, and the like; ophthalmic conditions associated with cell proliferation such as proliferative vitreoretinopathy; cutaneous diseases such as contact dermatitis, atopic dermatitis, urticaria, and other eczematoid dermatitis.

20 Tachykinin, and in particular substance P, antagonists may also be of use in the treatment of neoplasms, including breast tumours, neuroganglioblastomas and small cell carcinomas such as small cell lung cancer.

Tachykinin, and in particular substance P, antagonists may also be 25 of use in the treatment of gastrointestinal (GI) disorders, including inflammatory disorders and diseases of the GI tract such as gastritis, gastroduodenal ulcers, gastric carcinomas, gastric lymphomas, disorders associated with the neuronal control of viscera, ulcerative colitis, Crohn's disease, irritable bowel syndrome and emesis, including acute, delayed or 30 anticipatory emesis such as emesis induced by chemotherapy, radiation, toxins, viral or bacterial infections, pregnancy, vestibular disorders, for

example, motion sickness, vertigo, dizziness and Meniere's disease, surgery, migraine, variations in intracranial pressure, gastro-oesophageal reflux disease, acid indigestion, over indulgence in food or drink, acid stomach, waterbrash or regurgitation, heartburn, for example, episodic, 5 nocturnal or meal-induced heartburn, and dyspepsia.

Tachykinin, and in particular substance P, antagonists may also be of use in the treatment of a variety of other conditions including stress related somatic disorders; reflex sympathetic dystrophy such as shoulder/hand syndrome; adverse immunological reactions such as 10 rejection of transplanted tissues and disorders related to immune enhancement or suppression such as systemic lupus erythematosus; plasma extravasation resulting from cytokine chemotherapy, disorders of bladder function such as cystitis, bladder detrusor hyper-reflexia and incontinence; fibrosing and collagen diseases such as scleroderma and 15 eosinophilic fascioliasis; disorders of blood flow caused by vasodilation and vasospastic diseases such as angina, vascular headache, migraine and Reynaud's disease; and pain or nociception attributable to or associated with any of the foregoing conditions, especially the transmission of pain in migraine.

20 The compounds of formula (I) are also of value in the treatment of a combination of the above conditions, in particular in the treatment of combined post-operative pain and post-operative nausea and vomiting.

The compounds of formula (I) are particularly useful in the treatment of emesis, including acute, delayed or anticipatory emesis, such 25 as emesis induced by chemotherapy, radiation, toxins, pregnancy, vestibular disorders, motion, surgery, migraine, and variations in intracranial pressure. Most especially, the compounds of formula (I) are of use in the treatment of emesis induced by antineoplastic (cytotoxic) agents including those routinely used in cancer chemotherapy.

30 Examples of such chemotherapeutic agents include alkylating agents, for example, nitrogen mustards, ethyleneimine compounds, alkyl

sulphonates and other compounds with an alkylating action such as nitrosoureas, cisplatin and dacarbazine; antimetabolites, for example, folic acid, purine or pyrimidine antagonists; mitotic inhibitors, for example, vinca alkaloids and derivatives of podophyllotoxin; and cytotoxic antibiotics.

Particular examples of chemotherapeutic agents are described, for instance, by D. J. Stewart in *Nausea and Vomiting: Recent Research and Clinical Advances*, Eds. J. Kucharczyk *et al*, CRC Press Inc., Boca Raton, Florida, USA (1991) pages 177-203, especially page 188. Commonly used chemotherapeutic agents include cisplatin, dacarbazine (DTIC), dactinomycin, mechlorethamine (nitrogen mustard), streptozocin, cyclophosphamide, carmustine (BCNU), lomustine (CCNU), doxorubicin (adriamycin), daunorubicin, procarbazine, mitomycin, cytarabine, etoposide, methotrexate, 5-fluorouracil, vinblastine, vincristine, bleomycin and chlorambucil [R. J. Gralla *et al* in *Cancer Treatment Reports* (1984) 68(1), 163-172].

The compounds of formula (I) are also of use in the treatment of emesis induced by radiation including radiation therapy such as in the treatment of cancer, or radiation sickness; and in the treatment of post-operative nausea and vomiting.

It will be appreciated that the compounds of formula (I) may be presented together with another therapeutic agent as a combined preparation for simultaneous, separate or sequential use for the relief of emesis. Such combined preparations may be, for example, in the form of a twin pack.

A further aspect of the present invention comprises the compounds of formula (I) in combination with a 5-HT₃ antagonist, such as ondansetron, granisetron or tropisetron, or other anti-emetic medicaments, for example, a dopamine antagonist such as metoclopramide. Additionally, a compound of formula (I) may be administered in combination with an anti-inflammatory corticosteroid,

such as dexamethasone. Furthermore, a compound of formula (I) may be administered in combination with a chemotherapeutic agent such as an alkylating agent, antimetabolite, mitotic inhibitor or cytotoxic antibiotic, as described above. In general, the currently available dosage forms of the known therapeutic agents for use in such combinations will be suitable.

When tested in the ferret model of cisplatin-induced emesis described by F. D. Tattersall *et al*, in *Eur. J. pharmacol.*, (1993) 250, R5-R6, the compounds of the present invention were found to attenuate the retching and vomiting induced by cisplatin.

The compounds of formula (I) are also particularly useful in the treatment of pain or nociception and/or inflammation and disorders associated therewith such as, for example, neuropathy, such as diabetic and chemotherapy-induced neuropathy, postherpetic and other neuralgias, asthma, osteoarthritis, rheumatoid arthritis and headache, including migraine, acute or chronic tension headache, cluster headache, temporomandibular pain, and maxillary sinus pain.

The present invention further provides a compound of formula (I) for use in therapy.

According to a further or alternative aspect, the present invention provides a compound of formula (I) for use in the manufacture of a medicament for the treatment of physiological disorders associated with an excess of tachykinins, especially substance P.

The present invention also provides a method for the treatment or prevention of physiological disorders associated with an excess of tachykinins, especially substance P, which method comprises administration to a patient in need thereof of a tachykinin reducing amount of a compound of formula (I) or a composition comprising a compound of formula (I).

For the treatment of certain conditions it may be desirable to employ a compound according to the present invention in conjunction with another pharmacologically active agent. For example, for the treatment of

respiratory diseases such as asthma, a compound of formula (I) may be used in conjunction with a bronchodilator, such as a β_2 -adrenergic receptor antagonist or tachykinin antagonist which acts at NK-2 receptors. The compound of formula (I) and the bronchodilator may be 5 administered to a patient simultaneously, sequentially or in combination.

Likewise, a compound of the present invention may be employed with a leukotriene antagonists, such as a leukotriene D₄ antagonist such as a compound selected from those disclosed in European patent specification nos. 0 480 717 and 0 604 114 and in US patent nos. 4,859,692 10 and 5,270,324. This combination is particularly useful in the treatment of respiratory diseases such as asthma, chronic bronchitis and cough.

The present invention accordingly provides a method for the treatment of a respiratory disease, such as asthma, which method comprises administration to a patient in need thereof of an effective 15 amount of a compound of formula (I) and an effective amount of a bronchodilator.

The present invention also provides a composition comprising a compound of formula (I), a bronchodilator, and a pharmaceutically acceptable carrier.

It will be appreciated that for the treatment or prevention of 20 migraine, a compound of the present invention may be used in conjunction with other anti-migraine agents, such as ergotamines or 5-HT₁ agonists, especially sumatriptan.

Likewise, for the treatment of behavioural hyperalgesia, a 25 compound of the present invention may be used in conjunction with an antagonist of N-methyl D-aspartate (NMDA), such as dizocilpine.

For the treatment or prevention of inflammatory conditions in the lower urinary tract, especially cystitis, a compound of the present invention may be used in conjunction with an anti-inflammatory agent 30 such as a bradykinin receptor antagonist.

The present invention also provides a composition comprising a compound of formula (I), a bronchodilator, and a pharmaceutically acceptable carrier.

It will be appreciated that for the treatment or prevention of pain or 5 nociception, a compound of the present invention may be used in conjunction with other analgesics, such as acetaminophen (paracetamol), aspirin and other NSAIDs and, in particular, opioid analgesics, especially morphine. Specific anti-inflammatory agents include diclofenac, ibuprofen, indomethacin, ketoprofen, naproxen, piroxicam and sulindac. 10 Suitable opioid analgesics of use in conjunction with a compound of the present invention include morphine, codeine, dihydrocodeine, diacetylmorphine, hydrocodone, hydromorphone, levorphanol, oxymorphone, alfentanil, buprenorphine, butorphanol, fentanyl, sufentanyl, meperidine, methadone, nalbuphine, propoxyphene and 15 pentazocine; or a pharmaceutically acceptable salt thereof. Preferred salts of these opioid analgesics include morphine sulphate, morphine hydrochloride, morphine tartrate, codeine phosphate, codeine sulphate, dihydrocodeine bitartrate, diacetylmorphine hydrochloride, hydrocodone bitartrate, hydromorphone hydrochloride, levorphanol tartrate, 20 oxymorphone hydrochloride, alfentanil hydrochloride, buprenorphine hydrochloride, butorphanol tartrate, fentanyl citrate, meperidine hydrochloride, methadone hydrochloride, nalbuphine hydrochloride, propoxyphene hydrochloride, propoxyphene napsylate (2-naphthalenesulphonic acid (1:1) monohydrate), and pentazocine 25 hydrochloride.

Therefore, in a further aspect of the present invention, there is provided a pharmaceutical composition comprising a compound of the present invention and an analgesic, together with at least one pharmaceutically acceptable carrier or excipient.

30 In a further or alternative aspect of the present invention, there is provided a product comprising a compound of the present invention and

an analgesic as a combined preparation for simultaneous, separate or sequential use in the treatment or prevention of pain or nociception.

The excellent pharmacological profile of the compounds of the present invention offers the opportunity for their use in therapy at low doses thereby minimising the risk of unwanted side effects.

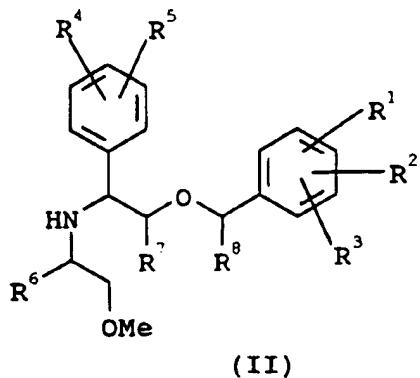
In the treatment of the conditions associated with an excess of tachykinins, a suitable dosage level is about 0.001 to 50 mg/kg per day, in particular about 0.01 to about 25 mg/kg, such as from about 0.05 to about 10 mg/kg per day.

For example, in the treatment of conditions involving the neurotransmission of pain sensations, a suitable dosage level is about 0.001 to 25 mg/kg per day, preferably about 0.005 to 10 mg/kg per day, and especially about 0.005 to 5 mg/kg per day. The compounds may be administered on a regimen of 1 to 4 times per day, preferably once or twice per day.

In the treatment of emesis using an injectable formulation, a suitable dosage level is about 0.001 to 10 mg/kg per day, preferably about 0.005 to 5 mg/kg per day, and especially 0.01 to 1 mg/kg per day. The compounds may be administered on a regimen of 1 to 4 times per day, preferably once or twice per day.

It will be appreciated that the amount of a compound of formula (I) required for use in any treatment will vary not only with the particular compounds or composition selected but also with the route of administration, the nature of the condition being treated, and the age and condition of the patient, and will ultimately be at the discretion of the attendant physician.

According to a general process (A), the compounds according to the invention may be prepared from compounds of formula (II)



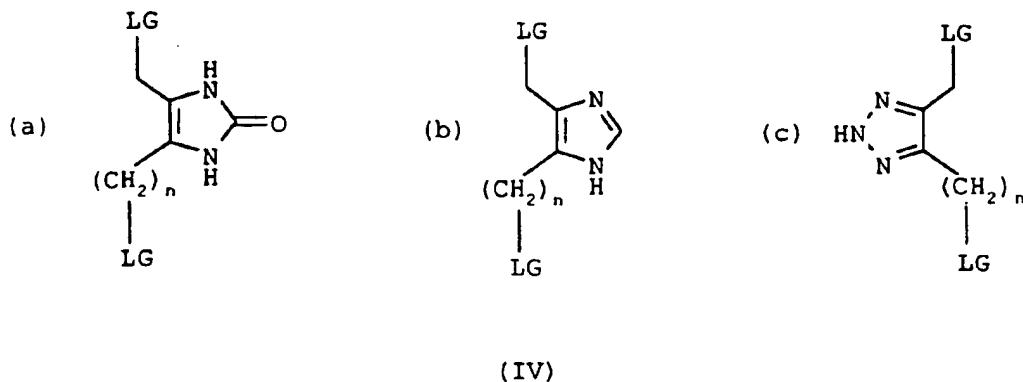
wherein R¹, R², R³, R⁴, R⁵, R⁶, R⁷ and R⁸ are as defined in relation to
5 formula (I) by reaction with a compound of formula (III):

LG-CH₂-Het'(III)

where Het' is a group of the formula Het as defined in relation to formula
10 (I) or a precursor therefor and LG is a leaving group such as an alkyl- or arylsulphonyloxy group (e.g. mesylate or tosylate) or a halogen atom (e.g. bromine, chlorine or iodine); and, if Het' is a precursor group, converting it to a group Het (in which process any reactive group may be protected and thereafter deprotected if desired).

15 This reaction may be performed in conventional manner, for example in an organic solvent such as dimethylformamide in the presence of an acid acceptor such as potassium carbonate.

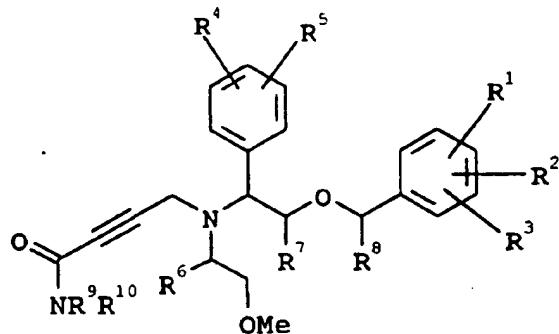
Thus, for instance, compounds in which Het is a 2-oxo-1,3-imidazolyl, 1,3-imidazolyl or 1,2,3-triazolyl group, each of which is
20 substituted by ZNR⁹R¹⁰, may be prepared by the reaction of a compound of formula (II) with a compound of formula (IV)



where n is an integer from 1 to 6, and each LG independently represents a leaving group as previously defined, followed by reaction of the resultant compound with an amine of formula $\text{NHR}^9\text{R}^{10}$ to complete the group $\text{ZNR}^9\text{R}^{10}$.

It will be appreciated that, where necessary, reactive groups may be protected, thus for example, the NH groups of an imidazolone of formula (IVa) may be protected by any suitable amine protecting group such as an acetyl group.

According to another process (B), compounds of formula (I) wherein Het represents 1,2,3-triazol-4-yl substituted by $\text{CH}_2\text{NR}^9\text{R}^{10}$, may be prepared by reaction of a compound of formula (V)



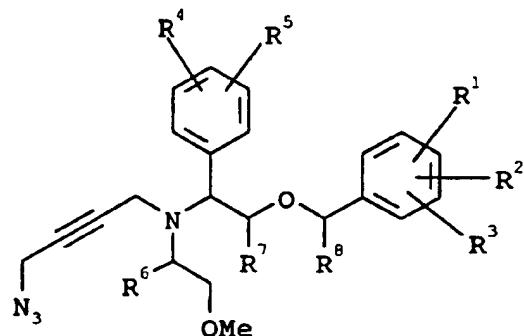
(V)

15

with an azide, for example, sodium azide in a suitable solvent such as dimethylsulphoxide at a temperature of between 40°C and 100°C, followed

by reduction of the carbonyl group adjacent to $\text{-NR}^9\text{R}^{10}$ using a suitable reducing agent such as lithium aluminium hydride at a temperature between -10°C and room temperature, conveniently at room temperature.

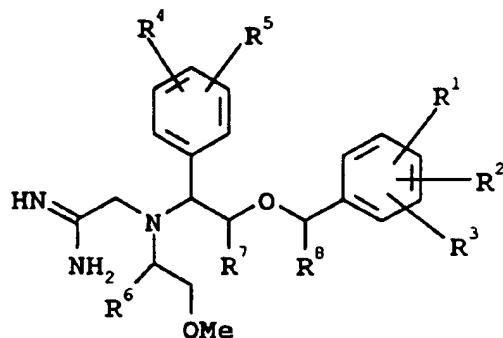
Alternatively, according to a process (C), compounds of formula (I) wherein Het represents 1,2,3-triazol-4-yl substituted by $\text{CH}_2\text{NR}^9\text{R}^{10}$, may be prepared by reaction of a compound of formula (VI)



(VI)

with an amine of formula $\text{NHR}^9\text{R}^{10}$, in a suitable solvent such as an ether, for example, dioxan, at elevated temperature, for example, between 50°C and 100°C , in a sealed tube, or the like. This reaction is based upon that described in *Chemische Berichte* (1989) 122, p. 1963.

According to another process, (D), compounds of formula (I) wherein Het represents substituted or unsubstituted 1,3,5-triazine may be prepared by reaction of intermediates of formula (VII):

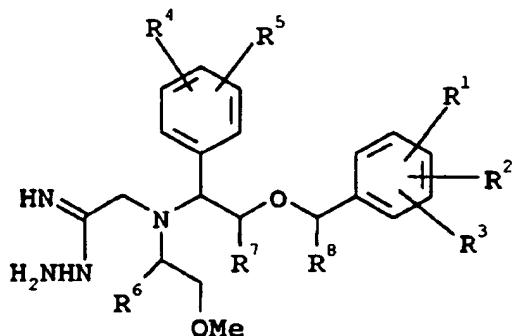


(VII)

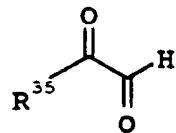
with substituted or unsubstituted 1,3,5-triazine.

The reaction is conveniently effected in a suitable organic solvent,
such as acetonitrile, at elevated temperature, such as 80-90°C, preferably
about 82°C.

According to a further process, (E), compounds of formula (I)
wherein Het represents substituted or unsubstituted 1,2,4-triazine may be
prepared by reaction of an intermediate of formula (VIII) with a
dicarbonyl compound of formula (IX):



(VIII)

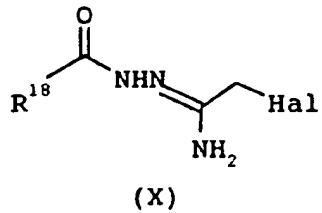


(IX)

wherein R³⁵ represents H or a suitable substituent such as ZNR⁹R¹⁰.

The reaction is conveniently effected in a suitable organic solvent,
such as an ether, e.g. tetrahydrofuran, conveniently at ambient
temperature.

According to a further process (F), compounds of formula (I) wherein Het represents a substituted 1,2,4-triazolyl group may be prepared by reaction of an intermediate of formula (II) with a compound of formula (X)



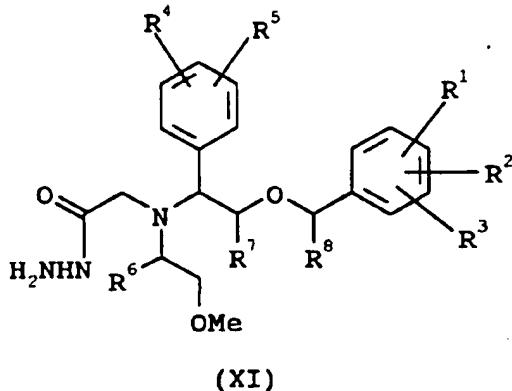
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wherein Hal is a halogen atom, for example, bromine, chlorine or iodine and R¹⁸ is H, CONH₂ or OCH₃ (which is converted to an oxo substituent under the reaction conditions), in the presence of a base, followed where necessary by conversion to a compound of formula (I), for example, by reduction of the CONH₂ group to CH₂NH₂.

Suitable bases of use in the reaction include alkali metal carbonates such as, for example, potassium carbonate. The reaction is conveniently effected in an anhydrous organic solvent such as, for example, anhydrous dimethylformamide, preferably at elevated temperature, such as about 140°C.

A suitable reducing agent for the group CONH₂ is lithium aluminium hydride, used at between -10°C and room temperature.

According to another process, (G), compounds of formula (I) wherein Het represents thioxotriazolyl may be prepared from intermediates of formula (XI)



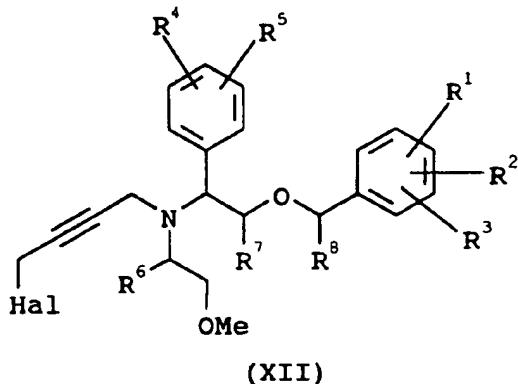
by reaction with a compound of formula HNCS, in the presence of a base.

Suitable bases of use in the reaction include organic bases such as, for example, 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU). The reaction is conveniently effected in a suitable organic solvent, such as alcohol, e.g. butanol.

Further details of suitable procedures will be found in the accompanying Examples.

Intermediates of formula (V) may be prepared from intermediates of formula (II) by reaction with an acetylene compound of formula HC≡C-CH₂-Hal in the presence of a base such as potassium carbonate in a suitable solvent such as dimethylformamide, conveniently at room temperature, followed by reaction of the resultant acetylene intermediate with an amide of formula Hal-CO-NR⁹R¹⁰ in the presence of suitable catalysts including bis(triphenylphosphine) palladium(II) chloride, copper(I) iodide and triphenylphosphine in a suitable solvent such as triethylamine, preferably at reflux.

Intermediates of formula (VI) may be prepared from a compound of formula (XII)



wherein Hal is a halogen atom, for example, chlorine, bromine or iodine, especially chlorine, by reaction with an azide, for example, sodium azide in a suitable solvent such as dimethylsulphoxide at or below room temperature.

Compounds of formula (XII) may be prepared by a dropwise addition of an intermediate of formula (II) to a dihaloacetylene of formula Hal-CH₂-C≡C-CH₂-Hal where each Hal is independently chlorine, bromine or iodine, especially chlorine. The reaction is conveniently effected in a suitable solvent such as dimethylformamide in the presence of a base such as potassium carbonate.

Intermediates of formula (VII) may be prepared from intermediates of formula (II) by reaction with a compound of formula Hal-CH₂-C(NH)NH₂, where Hal is as previously defined.

Intermediates of formula (VIII) may be prepared from intermediates of formula (II) by reaction with a compound of formula Hal-CH₂-C(NH)NHNH-Boc, wherein Hal is as previously defined and Boc stands for t-butoxycarbonyl, followed by deprotection under acidic conditions.

Compounds of formula (IX) are commercially available or may be prepared from commercially available compounds by known methods.

Compounds of formula (X) may be prepared as described in *J. Med. Chem.*, (1984) 27, 849.

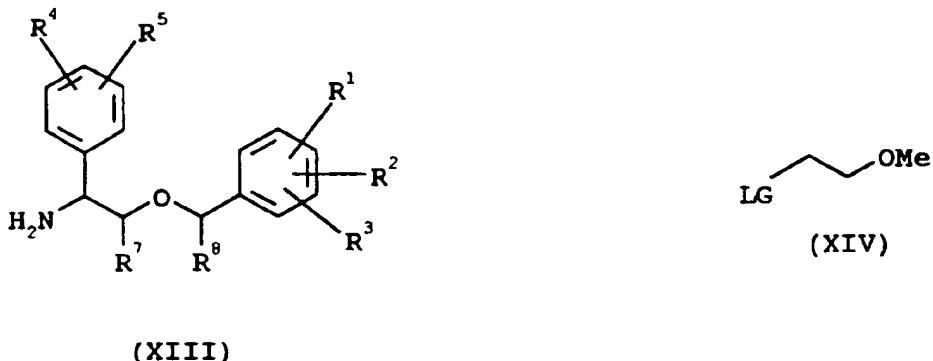
Intermediates of formula (XI) may be prepared from the corresponding ester by treatment with hydrazine. The reaction is conveniently effected in a suitable organic solvent, such as an alcohol, for example, ethanol, at elevated temperature.

5 For compounds wherein Het is a heterocycle substituted by a ZNR^9R^{10} group where Z is CH_2 , certain favoured compounds of formula (I) may be prepared from a corresponding compound with a hydrogen atom in place of the ZNR^9R^{10} . Thus, for example a compound of the formula (I) wherein Het is an imidazolinone group carrying a $CH_2NR^9R^{10}$ moiety may
10 be prepared from a corresponding compound lacking the $CH_2NR^9R^{10}$ moiety by reaction with formaldehyde and an amine NHR^9R^{10} under conventional Mannich reaction conditions, for example in methanol with heating. If desired a pre-formed reagent such as $R^9R^{10}N^+=CH_2.I^-$ may be employed and a tertiary amine such as triethylamine used as acid
15 acceptor.

Alternatively a compound of formula (I) wherein Het is an imidazolinone group lacking a $CH_2NR^9R^{10}$ may be reacted with paraformaldehyde and an amine for example a secondary amine such as pyrrolidine to give a compound wherein the imidazolinone ring is
20 substituted by $CH_2NR^9R^{10}$ where R^9 , R^{10} and the nitrogen atom to which they are attached form a heteroaliphatic ring of 4 to 7 ring atoms which may optionally contain an oxygen ring atom or a second nitrogen atom which will be part of a NH or NR^c moiety, where R^c is as previously defined.

25 This reaction may be performed in a conventional manner, for instance, in a suitable solvent such as an alcohol, for example, methanol at an elevated temperature up to the boiling point of the solvent.

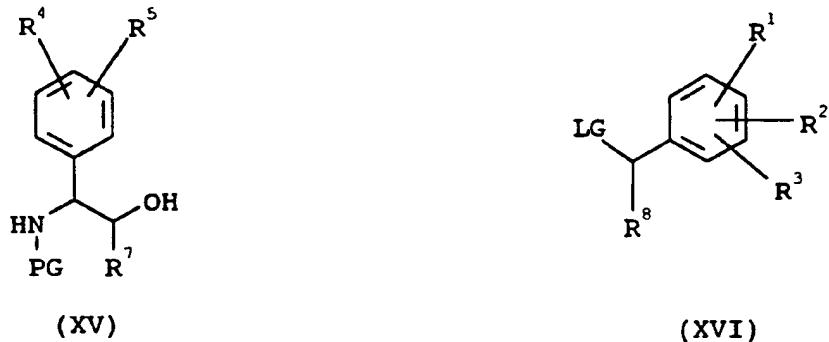
Intermediates of formula (II) may be prepared by reaction of a compound of formula (XIII) with a compound of formula (XIV):



wherein R^1 , R^2 , R^3 , R^4 , R^5 , R^7 and R^8 are as defined in relation to formula (I) and LG is as previously defined. Preferably LG is a halogen atom,
5 especially a bromine atom.

The reaction is effected in a conventional manner, for example in an organic solvent such as dimethylformamide in the presence of a base such as, for example, an alkali metal hydride, such as sodium hydride.

Compounds of formula (XIII) may be prepared from known starting
10 materials by the reaction of a compound of formula (XV) with a compound of formula (XVI), followed by removal of the N-protecting group:



15 where LG is as previously defined and PG is a conventional amine protecting group, such as *tert*-butoxycarbonyl. The reaction is conveniently effected in a suitable organic solvent, such as dimethylformamide in the presence of a base, such as, for example, an alkali metal hydride, such as sodium hydride. Removal of the protecting group

will depend upon the choice of protecting group. A tert-butoxycarbonyl group may be removed, for instance, using trifluoroacetic acid.

During any of the above synthetic sequences it may be necessary and/or desirable to protect sensitive or reactive groups on any of the molecules concerned. This may be achieved by means of conventional protecting groups, such as those described in *Protective Groups in Organic Chemistry*, ed. J.F.W. McOmie, Plenum Press, 1973; and T.W. Greene and P.G.M. Wuts, *Protective Groups in Organic Synthesis*, John Wiley & Sons, 1991. The protecting groups may be removed at a convenient subsequent stage using methods known from the art.

The exemplified compounds of this invention were tested by the methods set out at pages 36 to 39 of International Patent Specification No. WO 93/01165. The compounds were found to be active with IC₅₀ at the NK₁ receptor of less than 1μM on said test method.

The following non-limiting Examples serve to illustrate the preparation of compounds of the present invention:

EXAMPLE 1

4-(N-((2-((3,5-Bis(trifluoromethyl)phenyl)methyloxy)-1-(S)-phenyl)ethyl-N-(2'-methoxyethyl))aminomethyl)-5-(N,N'-dimethylaminomethyl)-1,2,3-triazole

a) (2S)-1-((3,5-Bis(trifluoromethyl)phenyl)methyloxy)-2-(2'-methoxyethylamino)-2-phenylethane

L-2-Ammonium-1-(3',5'-bis(trifluoromethyl)phenyl)methyloxy-2-phenylethane (2g) was dissolved in dimethylformamide (10ml). Sodium hydride (264mg, 60%) was added followed by 2-bromoethyl methyl ether (1.2g) and the mixture heated for 4 hours at 60°C. The reaction was quenched with water, extracted with ethyl acetate, washed with water (x2) and brine, dried (MgSO₄) and evaporated *in vacuo*. The residue was purified on silica gel eluting with 10% ethyl acetate/petroleum ether (60-

80°C) to give the title compound. ^1H NMR (250MHz, CDCl_3) δ 2.09 (1H, vbr s), 2.59-2.75 (2H, m), 3.35 (3H, s), 3.42-3.50 (2H, m), 3.54-3.64 (2H, m), 3.97 (1H, m), 4.62 (2H, s), 7.25-7.41 (5H, m), 7.76 (2H, s), 7.79 (1H, s).

5 b) (2S)-1-((3,5-Bis(trifluoromethyl)phenyl)methyloxy)-2-(N-(2'-methoxyethyl)-N-(4-chloro-2-butyne))amino-2-phenylethane

The product from step (a) (0.6g) was dissolved in dimethylformamide (6ml) and added dropwise to a pre-heated (60°C) solution of 1,4-dichloro-2-butyne (0.35g) and potassium carbonate (0.59g) in dimethylformamide (6ml). The mixture was stirred for 4 hours and was then extracted with ethyl acetate and water. The organic layer was washed (H_2O , brine), dried (MgSO_4) and evaporated *in vacuo*. The residue was purified on a gravity silica column using 10% ethyl acetate/petroleum ether (60-80°C) as eluant to give the title compound. ^1H NMR (250MHz, CDCl_3) δ 2.73 (2H, m), 3.23 (3H, s), 3.38 (2H, t, $J=5.8\text{Hz}$), 3.48 (1H, s), 3.56 (1H, s), 3.70-3.76 (1H, m), 3.81-3.91 (2H, m), 4.09 (2H, m), 7.19-7.29 (5H, m), 7.58 (2H, s), 7.68 (1H, s).

20 c) (2S)-1-((3,5-Bis(trifluoromethyl)phenyl)methyloxy)-2-(2'-methoxyethyl)-N-(4-azido-2-butyne)amino-2-phenylethane

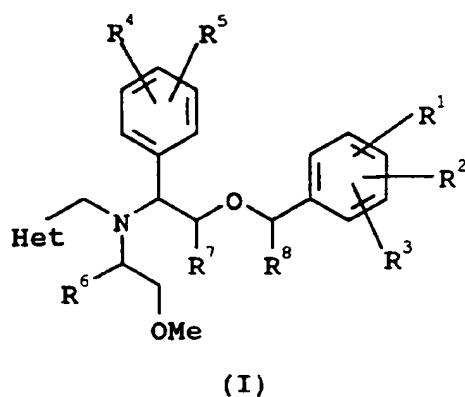
The product from step (b) (100mg) and sodium azide (16mg) were stirred together in dimethylsulfoxide under nitrogen for 16 hours. The reaction mixture was partitioned between ammonium chloride and ethyl acetate (4:1). The organic layer was washed (H_2O , brine), dried (MgSO_4) and evaporated *in vacuo*. The residue was purified on a gravity silica column using 20% ethyl acetate/ petroleum ether (60-80°C) as eluant to give the title compound. ^1H NMR (250MHz, CDCl_3) δ 2.72-2.81 (2H, m), 3.30 (3H, s), 3.41-3.48 (2H, m), 3.60 (1H, m), 3.62 (1H, br s), 3.75-4.00 (5H, m), 4.56 (2H, s), 7.26-7.40 (5H, m), 7.64 (2H, s), 7.75 (1H, s).

d) 4-((N-((2-((3,5-Bis(trifluoromethyl)phenyl)methoxy)-1-(S)-phenyl)ethyl-N-(2'-methoxyethyl))aminomethyl)-5-(N',N'-dimethylaminomethyl)-1,2,3-triazole

The product from step (c) (100mg) and dimethylamine (0.5ml) in 5 1,4-dioxane (2ml) was heated with stirring in a sealed tube at 70°C for 5 hours. The reaction mixture was then cooled and evaporated *in vacuo*. The residue was purified on a gravity silica column using 10%-20% methanol/ethyl acetate as eluant to give the title compound. ¹H NMR (250MHz, CDCl₃) δ 2.13 (6H, s), 2.66-2.75 (1H, m), 2.82-2.92 (1H, m), 3.27 10 (3H, s), 3.37-3.44 (4H, m), 3.77-3.83 (2H, m), 3.88-3.96 (2H, m), 4.05 (1H, t, J=6.29Hz), 4.54 (2H, s), 7.19-7.27 (5H, m), 7.64 (2H, s), 7.72 (1H, s). MS (ES) = 559.

CLAIMS:

1. A compound of the formula (I):



5

wherein

R¹ represents hydrogen, halogen, C₁₋₆alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, C₃₋₇cycloalkyl, C₃₋₇cycloalkylC₁₋₄alkyl, C₁₋₆alkoxy, C₁₋₄alkyl substituted by a hydroxy or C₁₋₄alkoxy group, OCF₃, hydroxy, trifluoromethyl, trimethylsilyl, nitro, CN, SR^a, SOR^a, SO₂R^a, COR^a, CO₂R^a or CONR^aR^b where R^a and R^b are each independently hydrogen or C₁₋₄alkyl;

10 R² and R³ each independently represent hydrogen, halogen, C₁₋₆alkyl, C₁₋₆alkoxy substituted by a C₁₋₄alkoxy group, or trifluoromethyl;

15 R⁴ represents hydrogen, halogen, C₁₋₆alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, C₃₋₇cycloalkyl, C₃₋₇cycloalkylC₁₋₄alkyl, C₁₋₆alkoxy, C₁₋₄alkyl substituted by a hydroxy or C₁₋₄alkoxy group, OCF₃, hydroxy, trifluoromethyl, trimethylsilyl, nitro, CN, SR^a, SOR^a, SO₂R^a, COR^a, CO₂R^a, CONR^aR^b where R^a and R^b are as previously defined;

20 R⁵ represents hydrogen, halogen, C₁₋₆alkyl, C₁₋₆alkoxy substituted by a C₁₋₄alkoxy group, or trifluoromethyl;

R⁶, R⁷ and R⁸ each independently represent hydrogen or a C₁₋₄alkyl group optionally substituted by a hydroxy group;

Het represents a 5- or 6-membered heterocyclic ring containing 2 or 3 nitrogen atoms optionally substituted by =O, =S or a C₁₋₄alkyl group, and optionally substituted by a group of the formula ZNR⁹R¹⁰ where

Z is C₁₋₆alkylene or C₃₋₆cycloalkyl;

5 R⁹ is hydrogen or C₁₋₄alkyl, C₃₋₇cycloalkyl,

C₃₋₇cycloalkylC₁₋₄alkyl, or C₂₋₄alkyl substituted by C₁₋₄alkoxy or hydroxyl;

R¹⁰ is hydrogen or C₁₋₄alkyl, C₃₋₇cycloalkyl,

C₃₋₇cycloalkylC₁₋₄alkyl, or C₂₋₄alkyl substituted by C₁₋₄alkoxy, hydroxyl or a 4, 5 or 6 membered heteroaliphatic ring containing one or two heteroatoms

10 selected from N, O and S;

or R⁹, R¹⁰ and the nitrogen atom to which they are attached form a heteroaliphatic ring of 4 to 7 ring atoms, optionally substituted by one or two groups selected from hydroxy or C₁₋₄alkoxy optionally substituted by a C₁₋₄alkoxy or hydroxyl group, and optionally containing a double bond,

15 which ring may optionally contain an oxygen or sulphur ring atom, a group S(O) or S(O)₂ or a second nitrogen atom which will be part of a NH or NR^c moiety where R^c is C₁₋₄alkyl optionally substituted by hydroxy or C₁₋₄alkoxy;

20 or R⁹, R¹⁰ and the nitrogen atom to which they are attached form a non-aromatic azabicyclic ring system of 6 to 12 ring atoms;

or Z, R⁹ and the nitrogen atom to which they are attached form a heteroaliphatic ring to 4 to 7 ring atoms which may optionally contain an oxygen ring atom;

or a pharmaceutically acceptable salt thereof.

25

2. A compound as claimed in claim 1 wherein R¹ is hydrogen, C₁₋₄alkyl, C₁₋₄alkoxy, halogen or CF₃.

30 3. A compound as claimed in claim 1 or claim 2 wherein R² is hydrogen, C₁₋₄alkyl, C₁₋₄alkoxy, halogen or CF₃.

4. A compound as claimed in any one of claims 1 to 3 wherein R³ is hydrogen, fluorine, chlorine or CF₃.

5. A compound as claimed in any one of claims 1 to 4 wherein R¹ and R² are in the 3 and 5 positions of the phenyl ring.

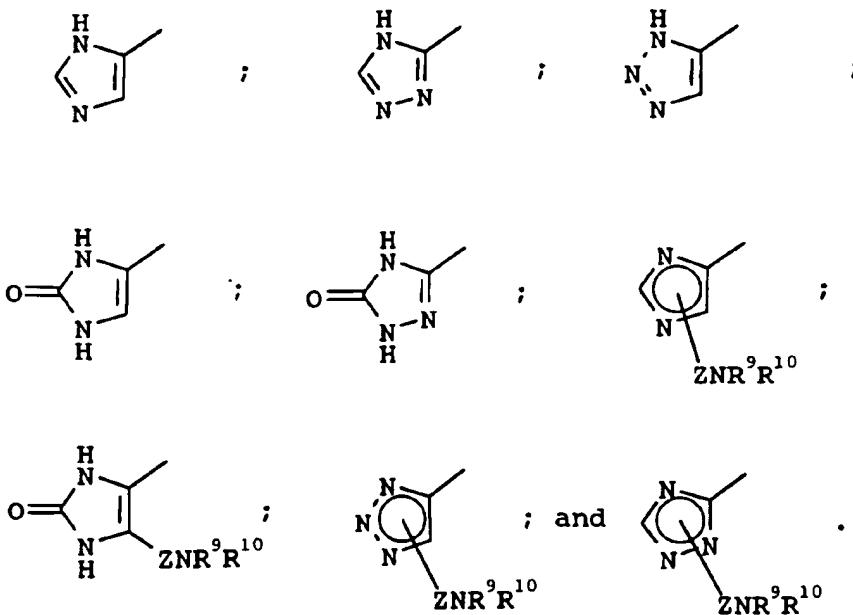
6. A compound as claimed in any one of claims 1 to 5 wherein R⁴ is hydrogen and R⁵ is hydrogen or 4-fluoro.

10 7. A compound as claimed in any one of claims 1 to 6 wherein R⁶ and R⁷ are each independently hydrogen or methyl.

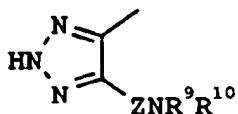
8. A compound as claimed in any one of claims 1 to 7 wherein R⁸ is hydrogen or C₁₋₂alkyl optionally substituted by a hydroxy group.

15

9. A compound as claimed in any one of claims 1 to 8 wherein Het represents a heterocyclic ring selected from:

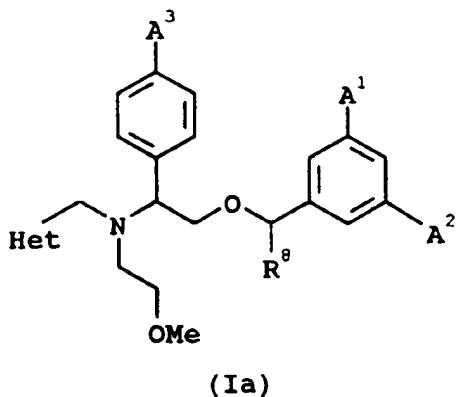


10. A compound as claimed in claim 9 wherein Het is:



11. A compound as claimed in any one of claims 1 to 10 wherein
Z is CH₂ or CH₂CH₂ and NR⁹R¹⁰ is amino, methylamino, dimethylamino,
5 diethylamino, azetidinyl, pyrrolidino and morpholino.

12. A compound of the formula (Ia):



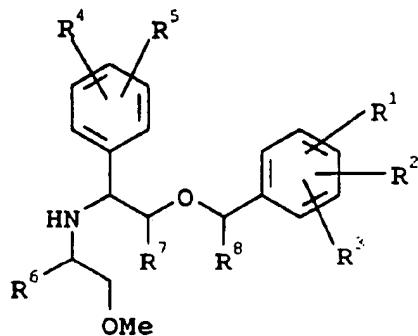
10

wherein R⁸ and Het are as defined in claim 1 and
A¹ is fluorine or CF₃;
A² is fluorine or CF₃; and
A³ is hydrogen or fluorine;
15 or a pharmaceutically acceptable salt thereof.

13. The compound:
4-(N-((2-((3,5-bis(trifluoromethyl)phenyl)methoxy)-1-(S-phenyl)ethyl-N-(2'-methoxyethyl))aminomethyl)-5-(N',N'-dimethylaminomethyl)-1,2,3-triazole;
20 or a pharmaceutically acceptable salt thereof.

14. A process for the preparation of a compound as claimed in any one of claims 1 to 13, which comprises

(A) reacting a compound of formula (II)



(II)

5

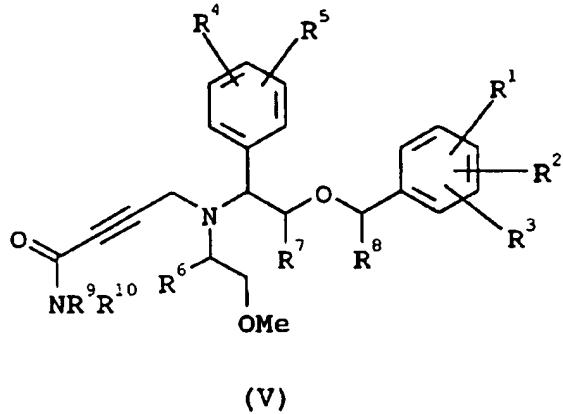
wherein R¹, R², R³, R⁴, R⁵, R⁶, R⁷ and R⁸ are as defined in claim 1 with a compound of formula (III):

10

LG-CH₂-Het' (III)

where Het' is a group of the formula Het as defined in claim 1 or a precursor therefor and LG is a leaving group such as an alkyl- or arylsulphonyloxy group or a halogen atom; and, if Het' is a precursor 15 group, converting it to a group Het; or

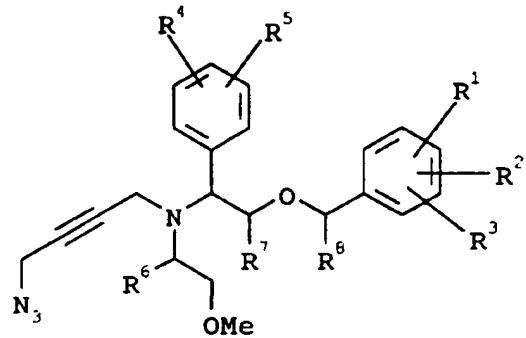
(B), where Het represents 1,2,3-triazol-4-yl substituted by CH₂NR⁹R¹⁰, by reaction of a compound of formula (V)



with an azide, followed by reduction of the carbonyl group adjacent to -NR⁹R¹⁰ using a suitable reducing agent; or

5

(C), where Het represents 1,2,3-triazol-4-yl substituted by CH₂NR⁹R¹⁰, by reaction of a compound of formula (VI)



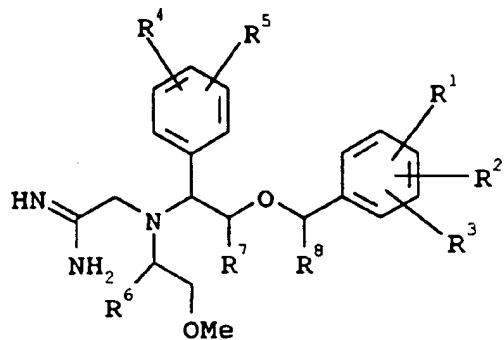
(VI)

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with an amine of formula NHR⁹R¹⁰; or

(D), where Het represents substituted or unsubstituted 1,3,5-triazine by reaction of intermediates of formula (VII):

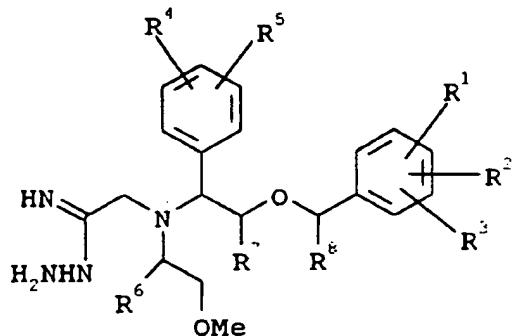
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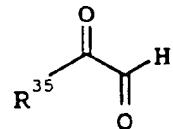
(VII)

with substituted or unsubstituted 1,3,5-triazine; or

5 (E), where Het represents substituted or unsubstituted 1,2,4-triazine by reaction of an intermediate of formula (VIII) with a dicarbonyl compound of formula (IX):



(VIII)

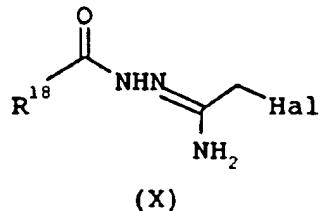


(IX)

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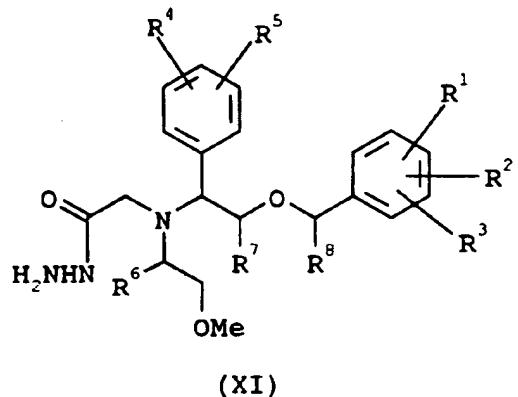
wherein R³⁵ represents H or ZNR⁹R¹⁰; or

(F), where Het represents a substituted 1,2,4-triazolyl group by reaction of an intermediate of formula (II) with a compound of formula (X)



wherein Hal is a halogen atom, and R¹⁸ is H, CONH₂ or OCH₃ (which is converted to an oxo substituent under the reaction conditions), in the presence of a base, followed where necessary by conversion to a compound 5 of formula (I); or

(G), where Het represents thioxotriazolyl from intermediates of formula (XI)



- 10 by reaction with a compound of formula HNCS, in the presence of a base;
each process being followed, where necessary, by the removal of any
protecting group where present;
and when the compound of formula (I) is obtained as a mixture of
enantiomers or diastereoisomers, optionally resolving the mixture to
15 obtain the desired enantiomer;
and/or, if desired, converting the resulting compound of formula (I)
or a salt thereof, into a pharmaceutically acceptable salt thereof.

15. A compound as claimed in any one of claims 1 to 13 for use in
20 therapy.

16. A pharmaceutical composition comprising a compound as claimed in any one of claims 1 to 13 in association with a pharmaceutically acceptable carrier or excipient.

5

17. A method for the treatment or prevention of physiological disorders associated with an excess of tachykinins, which method comprises administration to a patient in need thereof of a tachykinin reducing amount of a compound according to claim 1, or a pharmaceutically acceptable salt thereof, or a composition comprising a compound according to claim 1, or a pharmaceutically acceptable salt thereof.

18. A method according to claim 17 for the treatment or prevention of pain or inflammation.

19. A method according to claim 17 for the treatment or prevention of migraine.

20. A method according to claim 17 for the treatment or prevention of emesis.

21. A method according to claim 17 for the treatment or prevention of postherpetic neuralgia.

25

22. The use of a compound as claimed in any one of claims 1 to 13 for the manufacture of a medicament for the treatment or prevention of a physiological disorder associated with an excess of tachykinins.

23. The use of a compound as claimed in any one of claims 1 to 13
for the manufacture of a medicament for the treatment or prevention of
pain or inflammation.

5 24. The use of a compound as claimed in any one of claims 1 to 13
for the manufacture of a medicament for the treatment or prevention of
migraine.

10 25. The use of a compound as claimed in any one of claims 1 to 13
for the manufacture of a medicament for the treatment or prevention of
emesis.

15 26. The use of a compound as claimed in any one of claims 1 to 13
for the manufacture of a medicament for the treatment or prevention of
postherpetic neuralgia.

INTERNATIONAL SEARCH REPORT

International Application No

PCT/GB 96/00586

A. CLASSIFICATION OF SUBJECT MATTER

IPC 6 C07D249/04	A61K31/41	C07D247/00	C07D249/02	C07D251/02
		C07D253/02	A61K31/395	

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO,A,93 24465 (MERCK SHARP & DOHME LIMITED) 9 December 1993 see the whole document ---	1-26
A	EP,A,0 577 394 (MERCK & CO INC) 5 January 1994 cited in the application see the whole document -----	1-26

 Further documents are listed in the continuation of box C.

Patent family members are listed in annex.

* Special categories of cited documents :

- *A* document defining the general state of the art which is not considered to be of particular relevance
- *E* earlier document but published on or after the international filing date
- *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- *O* document referring to an oral disclosure, use, exhibition or other means
- *P* document published prior to the international filing date but later than the priority date claimed

T later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

X document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

Y document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

& document member of the same patent family

1

Date of the actual completion of the international search

19 June 1996

Date of mailing of the international search report

05. 07. 96

Name and mailing address of the ISA

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Authorized officer

Allard, M

INTERNATIONAL SEARCH REPORT

International application No.

PCT/GB96/00586

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reason:

1. Claims Nos.: because they relate to subject matter not required to be searched by this Authority, namely:
Although claims 17-21 are directed to a method of treatment of the human or animal body, the search has been carried out and based on the alleged effects of the compounds or compositions.
2. Claims Nos.: because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
3. Claims Nos.: because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest The additional search fees were accompanied by the applicant's protest. No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/GB 96/00586

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
WO-A-9324465	09-12-93	AU-B-	4084493	30-12-93
		US-A-	5494926	27-02-96
EP-A-0577394	05-01-94	AU-B-	4156893	06-01-94
		AU-B-	4656193	24-01-94
		CA-A-	2099233	30-12-93
		CN-A-	1087902	15-06-94
		CZ-A-	9403330	13-09-95
		FI-A-	946133	28-12-94
		HR-A-	931003	28-02-95
		HU-A-	71809	28-02-96
		JP-A-	6172178	21-06-94
		NO-A-	945064	28-02-95
		SI-A-	9300346	31-12-93
		SK-A-	160094	11-07-95
		WO-A-	9400440	06-01-94
		AU-B-	4160893	06-01-94
		ZA-A-	9304624	20-06-94